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Trial of Pregabalin for Acute and Chronic Sciatica

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ABSTRACT

BACKGROUND

Sciatica can be disabling, and evidence regarding medical treatments is limited. Pregabalin is effective in the treatment of some types of neuropathic pain. This study examined whether pregabalin may reduce the intensity of sciatica.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial of pregabalin in patients with sciatica. Patients were randomly assigned to receive either pregabalin at a dose of 150 mg per day that was adjusted to a maximum dose of 600 mg per day or matching placebo for up to 8 weeks. The primary outcome was the leg-pain intensity score on a 10-point scale (with 0 indicating no pain and 10 the worst possible pain) at week 8; the leg-pain intensity score was also evaluated at week 52, a secondary time point for the primary outcome. Secondary outcomes included the extent of disability, back-pain intensity, and quality-of-life measures at prespecified time points over the course of 1 year.

RESULTS

A total of 209 patients underwent randomization, of whom 108 received pregabalin and 101 received placebo; after randomization, 2 patients in the pregabalin group were determined to be ineligible and were excluded from the analyses. At week 8, the mean unadjusted leg-pain intensity score was 3.7 in the pregabalin group and 3.1 in the placebo group (adjusted mean difference, 0.5; 95% confidence interval [CI], −0.2 to 1.2; P=0.19). At week 52, the mean unadjusted leg-pain intensity score was 3.4 in the pregabalin group and 3.0 in the placebo group (adjusted mean difference, 0.3; 95% CI, −0.5 to 1.0; P=0.46). No significant between-group differences were observed with respect to any secondary outcome at either week 8 or week 52. A total of 227 adverse events were reported in the pregabalin group and 124 in the placebo group. Dizziness was more common in the pregabalin group than in the placebo group.

CONCLUSIONS

Treatment with pregabalin did not significantly reduce the intensity of leg pain associated with sciatica and did not significantly improve other outcomes, as compared with placebo, over the course of 8 weeks. The incidence of adverse events was significantly higher in the pregabalin group than in the placebo group. (Funded by the National Health and Medical Research Council of Australia; PRECISE Australian and New Zealand Clinical Trials Registry number, ACTRN12613000530729.)

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Sciatica is characterized by radiating posterior or posterolateral leg pain, which is sometimes accompanied by back pain, sensory loss, weakness, or reflex abnormalities.[1-3] Few clinical guidelines for the treatment of sciatica exist, and evidence regarding effective medical treatments is limited.[2,3]

Treatment with pregabalin (Lyrica, Pfizer) has been shown to be effective in reducing some types of neuropathic pain, including postherpetic neuralgia and diabetic peripheral neuropathy,[4,5] as well as allodynia and hyperalgesia from several conditions,[6-8] and some guidelines recommend pregabalin for the treatment of pain with neuropathic features.[5] Pregabalin therefore represents a potential treatment for sciatica. Its analgesic and antiepileptic properties have been attributed to binding to alpha 2–delta subunits of voltage-gated calcium channels, which results in decreased neurotransmitter release.[9]

One randomized, controlled trial in which the use of pregabalin was evaluated in patients with sciatica did not allow conclusions on efficacy because of limitations of the trial.[10] In that trial, only participants whose sciatica responded to treatment with pregabalin during a run-in period were enrolled, and half the participants in the placebo group had a violation of the trial protocol because their doses of pregabalin were tapered during the active trial phase. These issues potentially explained the similar short-term outcomes that were observed in the active treatment group and the placebo group. In addition, conflicting evidence exists regarding the use of a closely related antiepileptic drug, gabapentin, for sciatica.[11,12] Epidemiologic studies suggest that the use of pregabalin for pain that has neuropathic features has increased,[13,14] despite the lack of clear supporting evidence and despite concerns about an increased risk of suicidality as a potential side effect[15,16] and possible misuse of the drug.[17,18] We conducted a randomized, double-blind, placebo-controlled trial (Pregabalin in Addition to Usual Care for Sciatica [PRECISE]) to determine the efficacy, safety, and cost-effectiveness of pregabalin in patients with sciatica.

Methods

Trial Design and Oversight

In this randomized, double-blind, placebo-controlled trial, we compared pregabalin with placebo for the treatment of sciatica. The trial was conducted in accordance with the Consolidated Standards of Reporting Trials guidelines.[19] The trial protocol[20] and statistical analysis plan[21] have been published previously and are available with the full text of this article at NEJM.org. Ethics approval for the trial was granted by the University of Sydney Human Research Ethics Committee. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial was initiated by the investigators and was funded by the National Health and Medical Research Council of Australia. Pfizer Australia supplied the pregabalin capsules and matching placebo capsules at no cost and reviewed the manuscript before it was submitted; Pfizer Australia had no other involvement in either the conduct or the reporting of the trial. The investigators maintained full autonomy in the design, conduct, and reporting of the trial.

Eligibility and Recruitment

Patients who visited a trial clinician as an outpatient in New South Wales, Australia, for moderate-to-severe sciatica were considered for trial recruitment. Potential participants could also be screened by clinicians who were not involved in the trial (e.g., physiotherapists) and would then be referred to a trial clinician. Sciatica was defined in this trial as radiating pain into one leg below the knee, accompanied by nerve-root or spinal-nerve involvement as indicated by the presence of at least one of the following clinical features: dermatomal leg pain, myotomal weakness, sensory deficits, or diminished reflex, as determined by the trial clinician. Eligibility criteria also included a current episode of sciatica that had been present for a minimum of 1 week and a maximum of 1 year, leg pain that had been at least moderate in intensity or had resulted in at least moderate interference with daily activities during the previous week (as measured by modifications of items 7 and 8 in the Medical Outcomes Study 36-Item Short-Form Health Survey[22]), an age of at least 18 years, and either an adequate understanding of English or the availability of interpretation services for the participant to complete the trial.

Patients were excluded from participation in the trial if they had a known or suspected serious pathologic condition of the spine (e.g., the cauda equina syndrome); if they were pregnant, were breast-feeding, or were planning concep-

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tion (men [with their partners] and women) during the first 8 weeks of the trial; if they were considering or planning to undergo spinal surgery or other interventional procedures (e.g., a glucocorticoid injection) for sciatica during the first 8 weeks of the trial; if they had contraindications to pregabalin; if they were taking medication for neuropathic pain, antiepileptic medication, antidepressant medication, or sedative medication and were unable to cease taking such medications; or if they had severe depression or suicidal thoughts (a score of ≥20 on the Patient Health Questionnaire [scores range from 1 to 27, with scores of ≥20 indicating severe depression][23] or a score of 2 or 3 on question 9 [regarding suicidal thoughts] of the questionnaire). Trained trial clinicians explained the trial to each patient, obtained written informed consent from each patient, advised the research team that patients had been enrolled, and provided pregabalin or placebo to the patient.

RANDOMIZATION AND BLINDING

The randomization schedule was generated by an independent investigator by means of a computer-derived random-number sequence. Pregabalin capsules and matching placebo capsules were packaged in white, opaque, sealed containers at a central pharmacy according to the randomization schedule and were then supplied to the trial clinicians. All the research staff, statisticians, trial clinicians, and patients were unaware of the trial-group assignments during recruitment, data collection, and analysis.

TRIAL REGIMEN AND PROCEDURES

The trial regimen consisted of pregabalin or placebo as well as medical advice (e.g., advice to patients to avoid bed rest and to remain active and reassurance regarding the cause of symptoms and that symptoms usually diminish over time).[24] Each patient received up to nine weekly consultations with the trial clinician to begin taking the assigned regimen, to monitor progress, and to adjust the dose of pregabalin or placebo over the course of the first 8 weeks of the trial. The starting dose was 150 mg of pregabalin per day (75 mg twice daily) or matching placebo. The dose was adjusted to a maximum of 600 mg per day (300 mg twice daily), depending on the patient's progress and the side effects at each dose level as assessed by the trial clinician. In the standard trial regimen, the dose was increased each week for 3 weeks, from the starting dose of 150 mg per day to 300 mg per day, then to 450 mg per day, and then to a maintenance phase that was initiated at a dose of 600 mg per day for 4 weeks; subsequently, over the course of 1 week, the dose was gradually decreased and the regimen discontinued. If an adequate decrease in leg pain (e.g., leg pain rated as 0 or 1 for a minimum of 72 hours) was reported before the 8-week period was completed, the decrease in dose to subsequent cessation of the trial regimen could take place earlier.

Patients could receive additional medical care if it was considered to be suitable by the trial clinician. Such care could include physical therapies and could also include other analgesic medications (except for adjuvant analgesic agents), which would ideally be prescribed in accordance with the World Health Organization pain ladder.[25] Trial clinicians were asked not to prescribe certain medicines (antiepileptic medications, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine, and benzodiazepines) or to schedule interventional procedures. If the use of such medications or procedures was unavoidable, patients were permitted to stop taking pregabalin or placebo but could remain in the trial.

OUTCOMES AND DATA COLLECTION

The primary outcome was the average leg-pain intensity score over the course of the previous 24 hours (on a numerical pain-rating scale from 0 to 10, with 0 indicating no pain and 10 the worst possible pain; clinically important difference, 1.5 points), as assessed at 8 weeks; the leg-pain intensity score was also evaluated at week 52, a secondary time point for the primary outcome. Secondary outcomes were the extent of disability as measured on the Roland Disability Questionnaire for Sciatica (scores range from 0 to 23, with higher scores indicating greater disability; clinically important difference, 3 points), back-pain intensity (on a scale from 0 to 10, with higher scores indicating more pain), global perceived effect (current symptoms as compared with baseline, on a scale from –5 [vastly worse] to 0 [unchanged], to +5 [completely recovered]), quality of life as measured on the Short Form Health Survey 12, version 2 (on a scale from 0 to 100, with higher scores indicating better quality of life), workplace absenteeism, and health care

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utilization (i.e., the use of health services and medicines).

Data on serious adverse events and adverse events were collected. A serious adverse event was defined as any adverse event or reaction, regardless of causality, that resulted in death, was life-threatening, necessitated hospitalization, or was considered to be an important medical event. Other data that were collected included baseline demographic information, the PainDETECT score to screen for neuropathic pain,[26] satisfaction with the trial regimen, adherence to the prescribed doses of the trial regimen, and awareness of the trial-group assignment (patients were asked to report the trial group to which they believed they had been assigned). Outcomes were assessed at weeks 2, 4, 8 (primary time point of the primary outcome), 12, 26, and 52 (secondary time point of the primary outcome) either by means of telephone contact with the patients by trained trial researchers or by means of questionnaires that were completed by the patients directly through a secure online database.

STATISTICAL ANALYSIS

We determined that a minimum sample of 204 patients (102 per group) would be required to provide the trial with 90% power to detect a clinically important between-group difference of 1.5 points in the leg-pain intensity score on the 10-point numerical pain-rating scale at week 8 and to detect a clinically important between-group difference of 3 points out of 23 in the extent of disability on the Roland Disability Questionnaire for Sciatica[21] at week 8. Assumptions for the leg-pain intensity score and the extent of disability included a two-sided alpha level of 0.05 and a mean standard deviation of 2.5 points.[27] The estimated sample size would also allow for a withdrawal rate of 10% and a rate of nonadherence to the trial regimen of 20%.

Analyses were performed independently by two statisticians by means of dummy-group assignment and were based on the intention-to-treat principle. Two-sided P values of less than 0.05 were considered to indicate statistical significance. The primary outcome was analyzed with the use of repeated-measure linear mixed models that included all the leg-pain scores that were reported after randomization, with the baseline leg-pain score and the duration of leg pain as covariates. Adjusted mean differences were tested at week 8 (primary time point for the primary outcome) and at week 52 (secondary time point for the primary outcome). Within-patient correlations were modeled with the use of a compound symmetry covariance matrix. Similar analyses were applied to the secondary outcomes of extent of disability, back-pain intensity, global perceived effect, and quality of life. Unadjusted means and standard deviations were calculated for the primary outcome and for the secondary outcomes of extent of disability, back-pain intensity, global perceived effect, and quality of life.

Workplace absenteeism and health care utilization were calculated as the cumulative number of hours and the cumulative number of health services reported, respectively, between baseline and week 52, and were analyzed by means of analysis of covariance, with adjustment for the duration of leg pain at baseline. The use of medicines (excluding the trial regimen) was calculated as the percentage of patients who were reported to be taking at least one medicine for their leg pain and was compared between the trial groups with the use of Fisher's exact test. The number and incidence of serious adverse events and adverse events were reported descriptively, and the percentages of patients in each trial group who had at least one event were compared with the use of Fisher's exact test. Demographic and clinical characteristics at baseline, adherence to the trial regimen, assessment of awareness of the trial-group assignment, and satisfaction with the trial regimen were reported descriptively. Multiple imputations were not required because less than 10% of the primary-outcome data were missing.

Sensitivity analyses of the primary outcome and secondary outcomes (extent of disability, back-pain intensity, global perceived effect, and quality of life) were conducted by means of repeated-measure linear models with the use of heterogeneous compound symmetry and spatial power covariance. A subgroup analysis was conducted to assess whether the presence of neuropathic pain features, which had been identified by means of the PainDETECT questionnaire at baseline, was a modifier of treatment effect. In-depth statistical methods have been presented in the published statistical analysis plan.[21] Post hoc analyses included the addition of sex as a covariate to the main model and the analysis of workplace absenteeism in only those patients who had been employed at baseline. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

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RESULTS

PATIENTS

From September 2013 through March 2015, a total of 209 patients from 47 sites underwent randomization; 108 patients were randomly assigned to the pregabalin group and 101 to the placebo group (Fig. 1). After randomization, 2 patients in the pregabalin group were determined to be ineligible for the trial and were subsequently excluded because at the time of enrollment they were taking medicines that were not permitted.

The characteristics of the patients at baseline are presented in Table 1. At baseline, in the two trial groups, leg pain was most commonly related to the first sacral root (S1), with dermatomal pain being more predominant than neurologic deficit. The straight-leg raising maneuver induced pain in 63% of the patients in each group. The mean (±SD) leg-pain intensity score at baseline was 6.3±1.8 in the pregabalin group and 6.1±1.9 in the placebo group (Table 1). In total, 94% of patients in the pregabalin group and 92% of patients in the placebo group completed 8 weeks of the trial, and 86% of patients in each group completed 52 weeks of the trial.

EFFICACY

The mean difference between the two trial groups in the leg-pain intensity score was not significant at week 8 (unadjusted score, 3.7 in the pregabalin group and 3.1 in the placebo group; adjusted mean difference, 0.5; 95% confidence interval [CI], −0.2 to 1.2; P=0.19). The difference

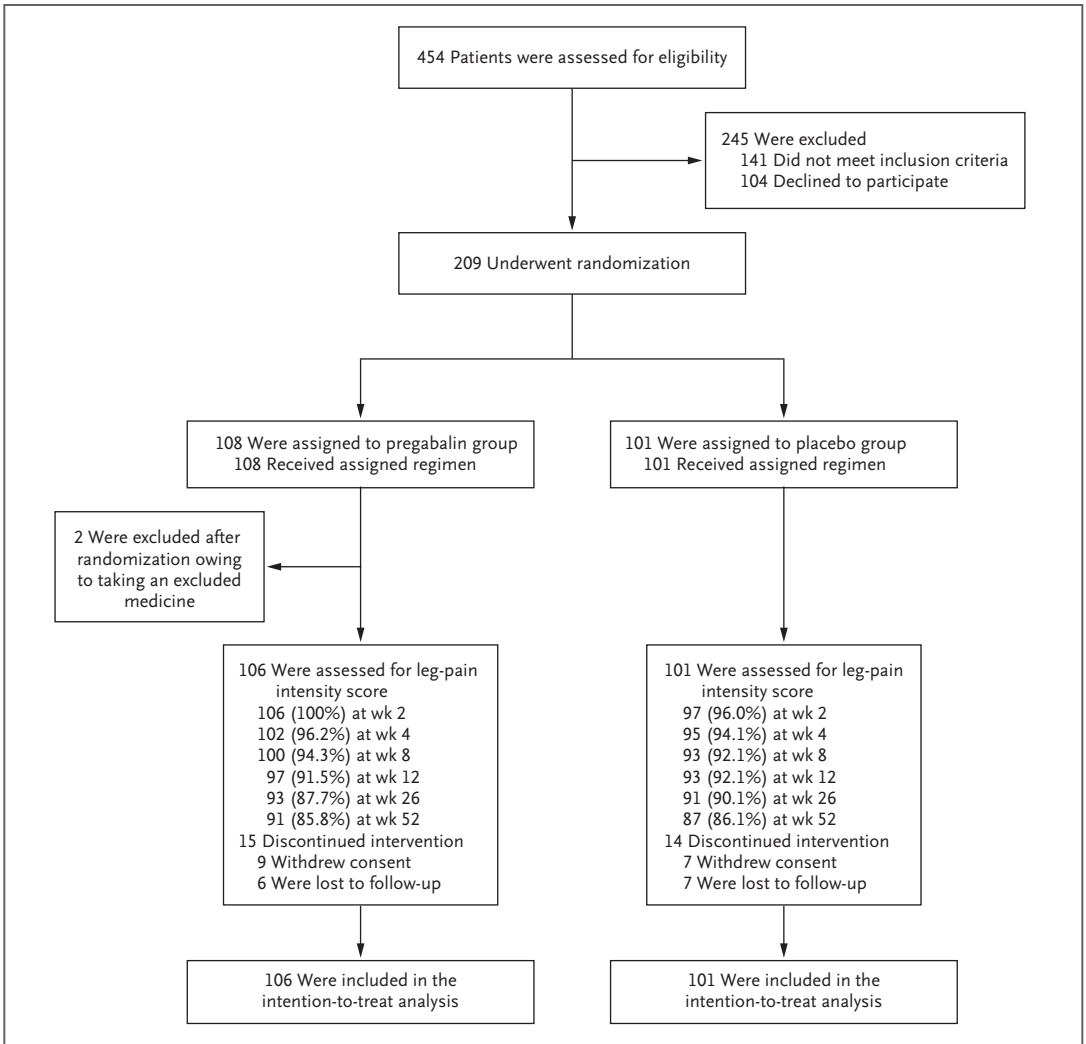
454 Patients were assessed for eligibility
245 Were excluded
141 Did not meet inclusion criteria
104 Declined to participate
209 Underwent randomization
108 Were assigned to pregabalin group
108 Received assigned regimen
101 Were assigned to placebo group
101 Received assigned regimen
2 Were excluded after randomization owing to taking an excluded medicine
106 Were assessed for leg-pain intensity score
106 (100%) at wk 2
102 (96.2%) at wk 4
100 (94.3%) at wk 8
97 (91.5%) at wk 12
93 (87.7%) at wk 26
91 (85.8%) at wk 52
15 Discontinued intervention
9 Withdrew consent
6 Were lost to follow-up
101 Were assessed for leg-pain intensity score
97 (96.0%) at wk 2
95 (94.1%) at wk 4
93 (92.1%) at wk 8
93 (92.1%) at wk 12
91 (90.1%) at wk 26
87 (86.1%) at wk 52
14 Discontinued intervention
7 Withdrew consent
7 Were lost to follow-up
106 Were included in the intention-to-treat analysis
101 Were included in the intention-to-treat analysis

Figure 1. Enrollment and Randomization of Patients with Sciatica.

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pregabalin Group (N=106)	Placebo Group (N=101)
Female sex — no. (%)	66 (62.3)	49 (48.5)
Age — yr	52.4±17.2	55.2±16.0
Dermatomal pain — no. (%)	93 (87.7)	82 (81.2)
Motor deficit — no. (%)	33 (31.1)	29 (28.7)
Neurologic deficit — no. (%)	42 (39.6)	34 (33.7)
Sensory deficit — no. (%)	47 (44.3)	44 (43.6)
Pain in both legs — no. (%)	11 (10.4)	7 (6.9)
Pain on straight-leg raising maneuver — no./total no. (%)†	52/83 (62.7)	54/86 (62.8)
Clinically suspected level of spine associated with leg pain — no. (%)		
L3	0	2 (2.0)
L4	20 (18.9)	30 (29.7)
L5	33 (31.1)	38 (37.6)
S1	54 (50.9)	43 (42.6)
S2	11 (10.4)	9 (8.9)
More than one level	17 (16.0)	25 (24.8)
Duration of leg pain — days	63.7±75.9	62.4±78.7
Leg-pain intensity score‡	6.3±1.8	6.1±1.9
Back-pain intensity score‡	5.9±2.8	5.1±3.0
Extent of disability score§	14.8±5.0	15.3±4.5
Global perceived effect score¶	−0.7±2.3	−1.0±2.3
Quality-of-life scores‖		
Physical component	36.2±9.4	36.5±9.6
Mental component	47.4±11.7	46.3±12.4
PainDETECT score — no. (%)**		
≤12	48 (45.3)	45 (44.6)
13–18	22 (20.8)	34 (33.7)
≥19	36 (34.0)	22 (21.8)

* Plus–minus values are means ±SD. A post hoc evaluation confirmed that there were no significant between-group differences in any of the characteristics at baseline.

† Pain on the straight-leg raising maneuver was not a condition of eligibility, but the test provided additional information, which was collected. Not all the trial clinicians reported findings of the straight-leg raising maneuver.

‡ Leg-pain intensity and back-pain intensity were measured by means of the numerical pain-rating scale, whereby patients were asked to rate their average pain over the previous 24 hours on a scale from 0 to 10, with 0 indicating no pain, and 10 indicating the worst possible pain.

§ The extent of disability was measured by means of the Roland Disability Questionnaire for Sciatica (scores range from 0 to 23, with higher scores indicating greater disability).

¶ For the assessment of global perceived effect, patients were asked to compare their current leg pain to the pain they had when this episode first started, as measured on a Likert scale; scores range from −5 (vastly worse) to 0 (unchanged) to +5 (completely recovered).

‖ Quality of life was measured by means of the Short Form Health Survey 12, version 2, questionnaire (scores on the physical and mental components of the questionnaire range from 0 to 100, with higher scores indicating a better quality of life).

** Scores on the PainDETECT questionnaire range from −1 to 38 and were divided into three categories to indicate the likelihood of neuropathic pain: a score of 12 or less indicated that a neurologic component was unlikely, a score of 13 to 18 that the status of a neurologic component was unclear, and a score of 19 or more that a neurologic component was likely.

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Table 2. Primary and Secondary Outcomes.*

Outcome and Time Point of Assessment	Adjusted Mean Difference (95% CI)	P Value
Leg-pain intensity		
At wk 8: primary outcome	0.5 (−0.2 to 1.2)	0.19
At wk 52: secondary time point for the primary outcome	0.3 (−0.5 to 1.0)	0.46
Secondary outcomes		
Extent of disability		
At wk 8	0.1 (−1.8 to 2.0)	0.96
At wk 52	0.2 (−1.8 to 2.2)	0.85
Back-pain intensity		
At wk 8	0.2 (−0.6 to 1.0)	0.56
At wk 52	0.6 (−0.2 to 1.5)	0.14
Global perceived effect		
At wk 8	−0.6 (−1.3 to 0.2)	0.15
At wk 52	−0.2 (−1.0 to 0.6)	0.69
Quality-of-life scores		
Physical component		
At wk 8	−0.7 (−3.5 to 2.1)	0.62
At wk 52	−1.2 (−4.1 to 1.6)	0.40
Mental component		
At wk 8	0.7 (−2.4 to 3.9)	0.65
At wk 52	0.1 (−3.2 to 3.3)	0.98

* This analysis was conducted with the use of a compound symmetry covariance structure. The adjusted mean differences represent the between-group differences for each outcome. A positive mean difference in the leg-pain intensity scores, the back-pain intensity scores, and the scores for the extent of disability favors the placebo group. A negative mean difference in the global perceived effect scores and the quality-of-life scores favors the placebo group.

was also not significant at week 52 (unadjusted score, 3.4 in the pregabalin group and 3.0 in the placebo group; adjusted mean difference, 0.3; 95% CI, −0.5 to 1.0; P=0.46) (Table 2, and Table S1 in the Supplementary Appendix, available at NEJM.org). Similarly, no effect of pregabalin, as compared with placebo, was observed in the following outcomes: the extent of disability at week 8 (adjusted mean difference, 0.1; 95% CI, −1.8 to 2.0; P=0.96) or at week 52 (adjusted mean difference, 0.2; 95% CI, −1.8 to 2.2; P=0.85); back-pain intensity at week 8 (adjusted mean difference, 0.2; 95% CI, −0.6 to 1.0; P=0.56) or at week 52 (adjusted mean difference, 0.6; 95% CI, −0.2 to 1.5; P=0.14); global perceived effect at week 8 (adjusted mean difference, −0.6; 95% CI, −1.3 to 0.2; P=0.15) or at week 52 (adjusted mean difference, −0.2; 95% CI, −1.0 to 0.6; P=0.69); quality-of-life physical component at week 8 (adjusted mean difference, −0.7; 95% CI, −3.5 to 2.1; P=0.62) or at week 52 (adjusted mean difference, −1.2; 95% CI, −4.1 to 1.6; P=0.40); or quality-of-life mental component at week 8 (adjusted mean difference, 0.7; 95% CI, −2.4 to 3.9; P=0.65) or at week 52 (adjusted mean difference, 0.1; 95% CI, −3.2 to 3.3; P=0.98) (Table 2). The unadjusted scores for the primary and secondary outcomes are provided in Table S1 in the Supplementary Appendix.

Figure 2 shows the time course of the adjusted scores for leg-pain intensity and the extent of disability. The results of other secondary outcomes are shown in Figure S1 in the Supplementary Appendix. The results of the primary and secondary outcomes were confirmed by the results of the sensitivity analyses (Table S2 in the Supplementary Appendix). The results of a subgroup analysis showed that the presence of neu-

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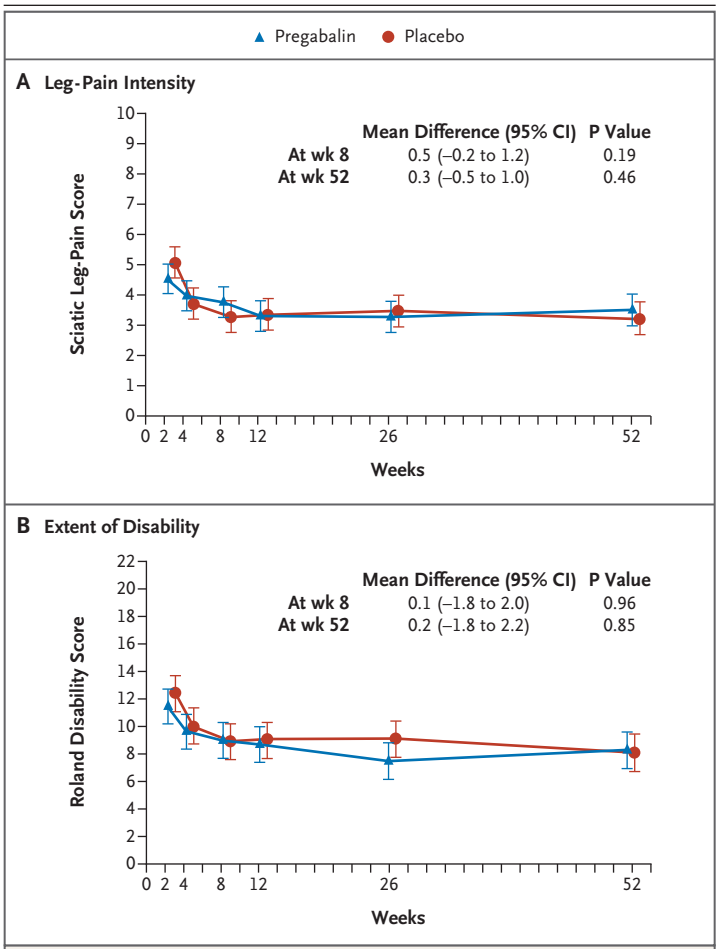
Pregabalin
Placebo
A Leg-Pain Intensity
Mean Difference (95% CI) P Value
At wk 8 0.5 (–0.2 to 1.2) 0.19
At wk 52 0.3 (–0.5 to 1.0) 0.46
Sciatic Leg-Pain Score
Weeks
B Extent of Disability
Mean Difference (95% CI) P Value
At wk 8 0.1 (–1.8 to 2.0) 0.96
At wk 52 0.2 (–1.8 to 2.2) 0.85
Roland Disability Score
Weeks

Figure 2. Time Course of Leg-Pain Intensity and Extent of Disability in Patients with Sciatica, According to Trial Group.

Panel A shows the unadjusted mean leg-pain intensity scores over time, as measured on a numerical pain-rating scale (scores range from 0 to 10, with 0 indicating no pain and 10 the worst possible pain). Panel B shows the unadjusted mean scores indicating the extent of disability over time, as measured on the Roland Disability Questionnaire for Sciatica scale (scores range from 0 to 23, with higher scores indicating greater disability). The mean differences were calculated with the use of a linear mixed model. I bars indicate standard deviations.

ropathic pain, as identified by the PainDETECT questionnaire, was not a modifier of the treatment effect on leg-pain intensity at week 8 (Table S4 in the Supplementary Appendix). A post hoc analysis confirmed that adjustment for sex had no effect on the primary outcome.

The mean difference between the pregabalin group and the placebo group in the number of hours that patients were absent from their workplace over the course of 1 year was not significant, either overall (mean difference, –50.6 hours; 95% CI, –109.5 to 8.2; P=0.09) or among patients who were employed at baseline (post hoc analysis mean difference, –97.6 hours; 95% CI, –213.8 to 18.6; P=0.10). Similarly, no significant difference was observed with respect to the percentages of patients who used additional medications for pain (72.5% in the pregabalin group and 66.0% in the placebo group, P=0.47) or the percentages of patients who used health services (68.4% and 61.7%, respectively; P=0.48) (Table S3 in the Supplementary Appendix). An economic evaluation was not conducted because no treatment effect was found, a condition that was prespecified in the statistical analysis plan.

SAFETY

The number of patients for whom serious adverse events were reported was similar in the two groups: 2 patients in the pregabalin group and 6 in the placebo group (P=0.16) (Table 3). The number of adverse events reported in the pregabalin group (227 events in 68 patients) was significantly higher than the number reported in the placebo group (124 events in 43 patients) (P=0.002) (Table 3). Dizziness was the most commonly reported adverse event in each group and was more common in the pregabalin group than in the placebo group (Table 3). The complete list of the adverse events reported during the trial is provided in Table S5 in the Supplementary Appendix.

OTHER VARIABLES

Approximately 74% of patients in each group were considered to have adhered to the dosing schedule (i.e., patients took ≥80% of their prescribed trial regimen; the mean patient-reported daily dose is summarized according to week in Table S6 in the Supplementary Appendix). Nearly two thirds of the patients in each group reported being either "extremely satisfied" or "satisfied" with the trial regimen. A lack of awareness of trial-group assignment was maintained; 48.1% of the patients were unaware of their group assignment, 23.0% incorrectly guessed their group assignment, and 29.0% correctly guessed their group assignment (Table S6 in the Supplementary Appendix).

DISCUSSION

This double-blind, placebo-controlled trial showed that pregabalin was no more effective than placebo in reducing leg-pain intensity in patients with moderate-to-severe sciatica of varying dura-

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Table 3. Adverse Events and Incidence of Pregnancy.*

Event	Pregabalin Group (N=106)		Placebo Group (N=101)		P Value
	no. of events	*no. of patients (%)*	*no. of events*	*no. of patients (%)*	
Serious adverse events					
Overall	2	2 (1.9)	6	6 (5.9)	0.16
Hospitalization for chest pain	0	0	1	1 (1.0)	
Hospitalization for dyspnea and nausea	1	1 (0.9)	0	0	
Hospitalization for increased back pain or leg pain	0	0	3	3 (3.0)	
Hospitalization for psychological distress	0	0	1	1 (1.0)	
Hospitalization for suicide attempt	0	0	1	1 (1.0)	
Suicidal thoughts	1	1 (0.9)	0	0	
Adverse events					
Overall	227	68 (64.2)	124	43 (42.6)	0.002
Most common					
Dizziness	70	42 (39.6)	19	13 (12.9)	
Dorsalgia	22	19 (17.9)	10	10 (9.9)	
Sweating	11	9 (8.5)	15	8 (7.9)	
Malaise	11	9 (8.5)	5	3 (3.0)	
Pregnancy†	1	1 (1.0)	2	2 (2.1)	

* A summary of all adverse events is provided in Table S5 in the Supplementary Appendix. Events were coded according to the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

† The incidence of pregnancy was assessed among 101 patients (or their partners in the case of male patients) in the pregabalin group and among 95 in the placebo group.

tions. Most patients had had sciatica for less than 3 months. Although the mean leg-pain intensity score decreased and secondary outcome measures improved over the course of the year in each trial group, the between-group difference was not significant for any outcome. The incidence of adverse events was higher in the pregabalin group than in the placebo group.

The trial was powered adequately to detect differences between the trial groups, and the between-group difference excluded a clinically important treatment effect of 1.5 points out of 10 for the leg-pain intensity score and a clinically important treatment effect of 3 points out of 23 for the assessment of the extent of disability.[28,29] The rate of adherence to the trial-regimen schedule and the rate of follow-up were both high. Our selection criteria were based on key clinical features of sciatica.[30] This approach enabled clinicians to enroll patients without the need for specialized equipment or imaging results, which allows for the generalizability of the trial findings. The dose of pregabalin that patients received was based on individual adjustment of the dose by the trial clinicians, which reflected the patient's progress and side effects, and adjustments were made in accordance with existing dosing recommendations, up to a dose of 600 mg per day.[31] Doses of 300 mg per day have been shown to reduce the acute neuropathic pain associated with diabetic peripheral neuropathy by 30%.[4]

Previous trials of pregabalin and gabapentin in patients with chronic low back pain or sciatica did not show a beneficial effect over placebo.[10,11] Our trial extends this finding by the inclusion of patients who had acute sciatica, with 80.2% of the cohort having had leg pain for less than 3 months. Our post hoc analyses showed that the duration of leg pain did not modify the effect of pregabalin among patients with sciatica. In contrast, pregabalin has been beneficial in the treatment of other types of neuropathic pain (e.g., painful polyneuropathy).[5] The lack of treatment effect of pregabalin in these patients with sciatica may

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reflect differences in pathophysiological features between other types of neuropathic pain and sciatica and suggests that the recommendations from guidelines regarding neuropathic pain may not extend to sciatica.

The incidence of serious adverse events among the patients who received pregabalin was similar to that observed in previous trials,[32] and we did not find a higher risk of suicidality with pregabalin than with placebo. However, this trial was not powered to detect the risk of suicidality as an outcome. Therefore, it is important that doctors continue to be cautious with regard to prescribing pregabalin to patients who are susceptible to self-harm.

In conclusion, our results show that pregabalin did not relieve sciatic pain or improve related clinical measures, as compared with placebo, over the course of 8 weeks. Pregabalin was associated with higher rates of adverse events than placebo.

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